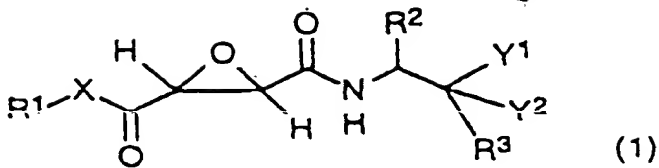


70620



wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^2 represents an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^3 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

X represents -O- or -NR⁴- in which R⁴ is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl

group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

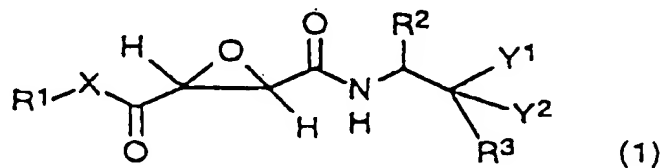
Y^1 represents a hydroxyl group, an alkoxy group having 1 to 6 carbon atoms, an acetoxy group, or an aralkyloxy group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y^2 represents a hydrogen atom or an alkyl group having 1 to 10 carbon atoms;

p^1
provided that the aryl group for R^1 to R^4 may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxy-carbonyl having 2-7 carbon atoms, $-CONH_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino; and

provided that the heterocyclic group for R^3 and R^4 is selected from the group consisting of pyridyl, pyrrolidinyl, piperidinyl, furyl, thienyl, piperazinyl, indolyl and benzimidazolyl.

p^2
7 ~~28~~. (Thrice Amended) An epoxysuccinamide derivative having the following formula (1) and its physiologically acceptable salt:



wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^2 represents an isobutyl group or an isopropyl group;

R^3 represents a hydrogen atom or an aryl group having 6 to 20 carbon atoms;

02
 X represents -O- or -NR⁴- in which R^4 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

Y^1 represents OR⁵ in which R^5 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, an acetoxy group, a benzoyloxy group, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y^2 represents a hydrogen atom;

provided that the alkyl group for R^5 may have one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, -CONH₂, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, and guanidino;

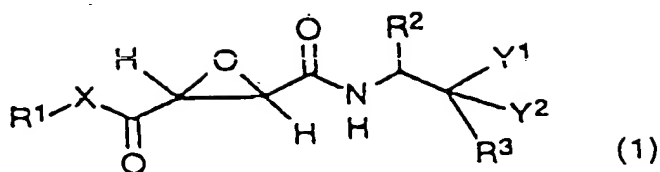
p²
provided that the aryl group for R¹, R³ and R⁵ may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, -CONH₂, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino;

provided that the heterocyclic group for R⁵ may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, -CONH₂, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino; and

provided that the heterocyclic group for R³, R⁴ and R⁵ is selected from the group consisting of pyridyl, pyrrolidinyl, piperidinyl, furyl, thienyl, piperazinyl, indolyl and benzimidazolyl.

D³
32. (Twice Amended) A method for treating a bone disease selected from the group consisting of osteoporosis, malignant hypercalcemia and Paget's disease, the method comprising injecting or orally administering into a patient an epoxysuccinamide derivative having the following formula (1) and its physiologically acceptable salt in an amount of 0.01 to 100 mg/day in the case of injection or in an amount of 0.1 mg/day to 1 g/day in the case of oral administration:

TO660



wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^2 represents an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^3 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

X represents -O- or -NR⁴- in which R⁴ is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl

0³

0³

0³

0³

0³

T0670



wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^2 represents an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^3 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

X represents -O- or -NR⁴- in which R⁴ is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

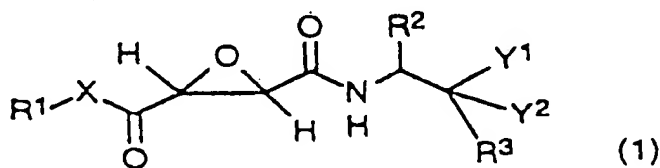
Y¹ represents a hydroxyl group, an alkoxy group having 1 to 6 carbon atoms, an acetoxy group, or an aralkyloxy group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y^2 represents a hydrogen atom or an alkyl group having 1 to 10 carbon atoms;

provided that the aryl group for R^1 to R^4 may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxy-carbonyl having 2-7 carbon atoms, $-\text{CONH}_2$, alkylamino-carbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino; and

D^3 provided that the heterocyclic group for R^3 and R^4 is selected from the group consisting of pyridyl, pyrrolidinyl, piperidinyl, furyl, thienyl, piperazinyl, indolyl and benzimidazolyl.

~~34~~¹⁴ (Thrice Amended) A method for treating a bone disease selected from the group consisting of osteoporosis, malignant hypercalcemia and Paget's disease, the method comprising injecting or orally administering into a patient an epoxysuccinamide derivative having the following formula (1) and its physiologically acceptable salt in an amount of 0.01 to 100 mg/day in the case of injection or in an amount of 0.1 mg/day to 1 g/day in the case of oral administration:



wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms,

an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^2 represents an isobutyl group or an isopropyl group;

R^3 represents a hydrogen atom or an aryl group having 6 to 20 carbon atoms;

X represents -O- or -NR⁴- in which R⁴ is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

Y^1 represents OR⁵ in which R⁵ is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, an acetoxy group, a benzyloxy group, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y^2 represents a hydrogen atom;

provided that the alkyl group for R⁵ may have one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, -CONH₂, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, and guanidino;

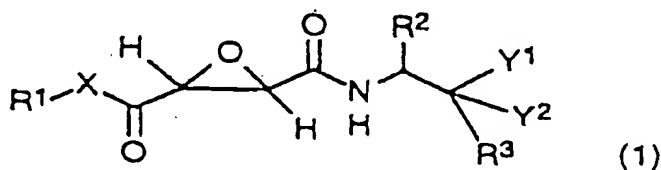
provided that the aryl group for R¹, R³ and R⁵ may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total,

alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, $-\text{CONH}_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino;

p^3 provided that the heterocyclic group for R^5 may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, $-\text{CONH}_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino; and

provided that the heterocyclic group for R^4 and R^5 is selected from the group consisting of pyridyl, pyrrolidinyl, piperidinyl, furyl, thienyl, piperazinyl, indolyl and benzimidazolyl.

~~15~~
~~38~~. (Thrice Amended) A method for treating arthritis which comprises injecting or orally administering into a patient an epoxysuccinamide derivative having the following formula (1) and its physiologically acceptable salt in an amount of 0.01 to 100 mg/day in the case of injection or in an amount of 0.1 mg/day to 1 g/day in the case of oral administration:



wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^2 represents an isobutyl group or an isopropyl group;

R^3 represents a hydrogen atom or an aryl group having 6 to 20 carbon atoms;

X represents -O- or -NR⁴- in which R^4 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

Y^1 represents OR⁵ in which R^5 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, an acetoxy group, a benzoyloxy group, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y^2 represents a hydrogen atom;

provided that the alkyl group for R^5 may have one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, -CONH₂, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, and guanidino;